Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supplementary Information

Diastereoselective synthesis of quaternary α-amino acids from diketopiperazine templates

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Experimental

General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[1] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or

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[1] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 1518.

a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General Procedure 1 for mono-lactim ether formation

A mixture of DKP (1.0 eq) and Me_3OBF_4 (2.0 eq) was stirred in $BmimBF_4$ for 96 h under vacuum before quenching with sat aq $NaHCO_3$ solution. The product was extracted with Et_2O, dried, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 2 for mono-lactim ether alkylation

BuLi (solution in hexanes, 1.0 eq) was added dropwise to a stirred solution of template (1.0 eq) in THF at −78°C. After 45 minutes, the electrophile (1.1 eq) was added dropwise *via* syringe. The reaction solution was then allowed to warm slowly to rt. After 16 h, the reaction mixture was quenched with sat aq NH_4Cl solution and stirred for a further 10 minutes. The product was then extracted with EtOAc, washed with H_2O, dried, concentrated *in vacuo* and purified by flash column chromatography.

General Procedure 3 for lactim-ether hydrolysis

The alkylated template was dissolved in TFA and subjected to reflux for 4 days. After this time the solvent was removed *in vacuo*. The remaining solid residue was triturated with Et_2O, filtered under suction and then dried under vacuum.

General Procedure 4 for DKP hydrolysis

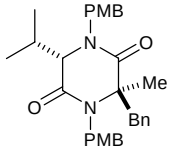
The DKP was dissolved in conc aq HCl and subjected to reflux for 3 days. Concentration of the reaction mixture *in vacuo* yielded a mixture of amino acid hydrochloride salts which were dried under vacuum.

General procedure 5 for formation of amino acid methyl esters

$SOCl_2$ (3.0 eq) was added to a solution of amino acid hydrochloride salts (1.0 eq) in MeOH at 0˚C, and subsequently set at reflux. After 16 h this solution was concentrated *in vacuo* to yield a mixture of amino acid methyl ester hydrochloride salts. This mixture was taken up into an aq solution and conc aq NH_3 was added dropwise until pH 10 was reached when it was extracted with DCM. The combined organic extracts

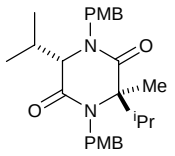
were dried and concentrated *in vacuo* to furnish a mixture of amino acid methyl esters. Valine methyl ester was distilled off under vacuum yielding the desired amino acid methyl ester.

(3*R*,6*S*)-*N*(1),*N*(4)-Bis-*p*-methoxybenzyl-3-benzyl-3-methyl-6-*iso*-propyl-piperazine-2,5-dione 7



KHMDS (0.5 M in toluene, 1.47 mL, 0.731 mmol) was added dropwise to a stirred solution of DKP **3** (100 mg, 0.244 mmol) in THF (10 mL) at –78˚C. After 45 minutes, BnBr (58 μL, 0.487 mmol) was added dropwise *via* syringe. The reaction solution was then allowed to warm slowly to rt. After 16 h, the reaction mixture was quenched with sat aq NH_4Cl solution and stirred for a further 10 minutes. The product was then extracted with EtOAc, washed with H_2O, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 1:1 40-60° petrol:Et_2O) gave **7** as a colourless oil (71 mg, 58%, 88% de); ν_{max} (film) 2961, 2836, 1643, 1513; δ_H (400 MHz; $CDCl_3$) 0.67 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.90 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.75 (3H, s, C(3)*Me*), 2.07 (1H, m, CH$_3$C*H*CH$_3$), 3.19 (1H, d, *J* 3.3, C(6)*H*), 3.26 (1H, d, *J* 14.1, C*H*HPh), 3.32 (1H, d, *J* 14.1, CH*H*Ph), 3.78 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.84 (1H, d, *J* 14.9, C*H*HAr), 4.18 (1H, d, *J* 14.7, C*H*HAr), 5.01 (1H, d, *J* 14.9, CH*H*Ar), 5.35 (1H, d, *J* 14.7, CH*H*Ar), 6.53-7.43 (13H, m, *Ar*, *Ph*); δ_C (50 MHz; $CDCl_3$) 16.0, 19.5, 27.5, 30.0, 44.6, 45.9, 46.6, 55.1, 61.6, 66.8, 113.7, 114.0, 126.6, 127.2, 128.5, 128.8, 129.6, 129.8, 130.0, 130.2, 130.4, 135.7, 159.0, 159.2, 165.5, 169.2; *m/z* (APCI$^+$) 501 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{31}H_{37}N_2O_4$ ([M+H]$^+$) requires 501.2753; found 501.2756.

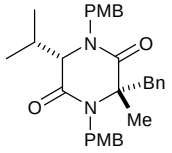
(3*R*,6*S*)-*N*(1),*N*(4)-Bis-*p*-methoxybenzyl-3,6-di-*iso*-propyl-3-methyl-piperazine-2,5-dione 8



KHMDS (0.5 M in toluene, 1.47 mL, 0.731) was added dropwise to a stirred solution of DKP **3** (100 mg, 0.244 mmol) in THF (10 mL) at –78˚C. After 45 minutes, ^{i}PrI (74 μL, 0.731 mmol) was added dropwise *via* syringe. The reaction solution was then allowed to warm slowly to rt. After 16 h, the reaction mixture was quenched with sat aq NH_4Cl solution and stirred for a further 10 minutes. The product was then extracted with EtOAc, washed with H_2O, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 1:1 Et_2O:cyclohexane) gave **8** as a white solid (40 mg, 36%, 86% de); mp

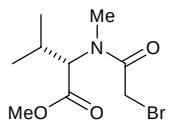
119°C; ν_{max} (KBr) 3435, 1653, 1512, 1246; δ_H (400 MHz; $CDCl_3$) 0.72 (3H, d, *J* 7.2, C*H*$_3$CHCH$_3$), 0.73 (3H, d, *J* 7.2, CH$_3$CHC*H*$_3$), 1.02 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.09 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.72 (3H, s, C(3)*Me*), 2.15 (1H, m, CH$_3$C*H*CH$_3$), 2.28 (1H, m, CH$_3$C*H*CH$_3$), 3.78 (1H, d, *J* 4.7, C(6)*H*), 3.78 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.87 (1H, d, *J* 14.5, C*H*HAr), 4.27 (1H, d, *J* 14.7, C*H*HAr), 4.66 (1H, d, *J* 14.7, CH*H*Ar), 5.32 (1H, d, *J* 14.5, CH*H*Ar), 6.79-7.33 (13H, m, *Ar*); δ_C (100 MHz; $CHCl_3$) 16.1, 17.5, 18.1, 19.8, 24.4, 30.4, 37.5, 45.6, 46.7, 55.2, 55.3, 62.4, 68.0, 113.4, 113.6, 114.1, 114.2, 127.4, 129.9, 130.3, 130.4, 158.5, 159.2, 165.9, 167.5; *m/z* (APCI$^+$) 453 ([M+H]$^+$, 6%), 121 (100); HRMS (ESI$^+$) $C_{27}H_{37}N_2O_4^+$ ([M+H$^+$]) requires 453.2753; found 453.2731.

(3*S*,6*S*)-*N*(1),*N*(4)-Bis-*p*-methoxybenzyl-3-benzyl-3-methyl-6-*iso*-propyl-piperazine-2,5-dione 9



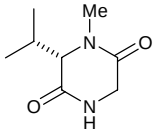
KHMDS (0.5 M in toluene, 15.0 mL, 7.49 mmol) was added dropwise to a stirred solution of DKP **4** (1.21 g, 2.50 mmol) in THF (120 mL) at –78˚C. After 45 minutes, MeI (1.55 mL, 25.0 mmol) was added dropwise *via* syringe. The reaction solution was then allowed to warm slowly to rt. After 16 h, the reaction mixture was quenched with sat aq NH_4Cl solution and stirred for a further 10 minutes. The product was then extracted with EtOAc, washed with H_2O, dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 1:1 Et_2O:cyclohexane) gave **9** as a colourless oil (987 mg, 79%, 81% de); ν_{max} (film) 3018, 1651, 1513, 1218; δ_H (400 MHz; $CDCl_3$) 0.65 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.97 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.51 (1H, m, CH$_3$C*H*CH$_3$), 1.52 (3H, s, C(3)*Me*), 3.14 (1H, d, *J* 14.0, C(3)C*H*HPh), 3.38 (1H, d, *J* 13.9, C(3)CH*H*Ph), 3.71 (1H, d, *J* 5.0, C(6)*H*), 3.78 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.86 (1H, d, *J* 14.8, C*H*HAr), 4.02 (1H, d, *J* 15.7, C*H*HAr), 5.06 (1H, d, *J* 15.6, CH*H*Ar), 5.44 (1H, d, *J* 14.8, CH*H*Ar), 6.78-7.31 (13H, m, *Ar*, *Ph*); δ_C (100 MHz; $CHCl_3$) 18.7, 21.1, 26.9, 35.6, 44.3, 46.4, 49.0, 55.2, 55.3, 63.7, 66.8, 127.4, 128.1, 128.7, 129.2, 130.6, 135.7, 158.4, 159.2, 166.7, 169.1; *m/z* (APCI$^+$) 501 ([M+H]$^+$, 8%), 121 (100); HRMS (ESI$^+$) $C_{31}H_{37}N_2O_4^+$ ([M+H$^+$]) requires 501.2753; found 501.2749.

(*S*)-*N*-(2-Bromoacetyl)-*N*-methyl-valine methyl ester 14



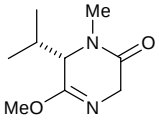
A solution of *N*-methyl-valine methyl ester **12** (2.52 g, 17.4 mmol) and Et_3N (2.90 mL, 20.9 mmol) in DCM (20 mL) was added dropwise over 1 h to a solution of bromoacetyl bromide (2.26 mL, 26.1 mmol) in DCM (60 mL) at −78°C. The reaction mixture was allowed to warm to rt over 16 h, washed with H_2O (100 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent hexane:Et_2O 2:1) gave **14** (3.68 g, 80%); $[\alpha]_D^{21}$ −103.4 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 1740, 1654; δ_H (500 MHz, PhMe-d_8, 373K) 0.79 (3H, d, *J* 6.7, C*H*$_3$CHCH$_3$), 0.89 (3H, d, *J* 6.4, CH$_3$CHC*H*$_3$), 2.06-2.15 (1H, m, CH$_3$C*H*CH$_3$), 2.80 (3H, s, N*Me*), 3.44 (3H, s, O*Me*), 3.65 (2H, s, C*H*$_2$Br), 3.85 (1H, app br s, ^{i}PrC*H*); δ_C (125 MHz, PhMe-d_8, 373K) 18.9, 19.7, 26.4, 28.3, 30.6, 51.2, 62.9, 167.0, 170.7; *m*/z (ESI$^+$) 290 ([M+Na]$^+$, ^{81}Br, 40%), 288 (40); HRMS (ESI$^+$) $C_9H_{17}BrNO_3$ ([M+H]$^+$, ^{79}Br) requires 266.0392; found 266.0393.

(*S*)-*N*(4)-Methyl-3-*iso*-propyl-piperazine-2,5-dione 16



14 (5.58 g, 21.0 mmol) was added to ethanol (200 mL) saturated with ammonia gas and stirred for 48 h. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL), the aqueous layer was separated and the organic layer was washed with H_2O (200 mL), dried and concentrated *in vacuo* to give **16** (2.86 g, 80%) as an orange crystalline solid; mp 74-75°C; $[\alpha]_D^{23}$ +103.7 (*c* 1.2 in $CHCl_3$); ν_{max} (KBr) 3206, 1658; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 1.05 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.14-2.25 (1H, m, CH$_3$C*H*CH$_3$), 2.94 (3H, s, N*Me*), 3.58 (1H, d, *J* 4.8, C(3)*H*), 3.81 (1H, dd, *J* 17.6, 4.0, C(6)*H*H), 3.95 (1H, d, *J* 17.6, C(6)*H*H) 7.44 (1H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) 18.0, 19.3, 32.2, 34.4, 45.0, 68.4, 164.8, 167.7; *m*/z (APCI$^+$) 171 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{15}N_2O_2$ ([M+H]$^+$) requires 171.1134; found 171.1137.

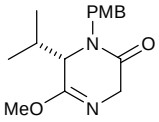
(*S*)-*N*(1)-Methyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 18



Following *General Procedure 1*, DKP **16** (2.53 g, 14.9 mmol) and Me_3OBF_4 (4.40 mg, 29.8 mmol) in $BmimBF_4$ (15 mL) gave, after purification *via* flash column chromatography (eluent EtOAc), **18** as a colourless oil (1.66 g, 61%); $[\alpha]_D^{23}$ +190.3 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1695, 1657; δ_H (400 MHz, $CDCl_3$)

0.68 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.80 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.94-2.02 (1H, m, CH$_3$C*H*CH$_3$), 2.74 (3H, s, N*Me*), 3.45 (3H, s, O*Me*), 3.53 (1H, m, C(6)*H*), 3.79 (1H, dd, *J* 20.8, 1.2, C(3)*H*H), 3.88 (1H, dd, *J* 20.8, 1.2, C(3)H*H*); δ_C (100 MHz, $CDCl_3$) 17.5, 19.0, 31.7, 33.2, 50.4, 52.5, 65.0, 160.5, 167.7; *m/z* (ESI$^+$) 185 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{17}N_2O_2$ ([M+H]$^+$) requires 185.1290; found 185.1287.

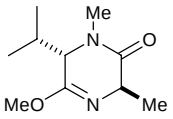
(*S*)-*N*(1)-*p*-Methoxybenzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 19



Following *General Procedure 1*, DKP **17** (6.20 g, 22.4 mmol) and Me_3OBF_4 (6.64 g, 44.9 mmol) in $BmimBF_4$ (30 mL) gave, after purification *via* flash column chromatography (eluent Et_2O), **19** as a pale brown crystalline solid (1.66 g, 61%); mp 94-96 °C (DCM-heptane); $[\alpha]_D^{23}$ +23.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1697, 1658; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.4, C*H*$_3$CHCH$_3$), 1.02 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.16-2.24 (1H, m, CH$_3$C*H*CH$_3$), 3.67 (3H, s, C(5)O*Me*), 3.69 (1H, ddd, *J* 2.0, 1.1, 1.0, C(6)*H*), 3.82 (3H, s, ArO*Me*), 3.84 (1H, d, *J* 14.9, NC*H*HAr), 4.12 (1H, dd, *J* 19.6, 1.1, C(3)*H*H), 4.24 (1H, dd, *J* 19.6, 1.0, C(3)H*H*), 5.42 (1H, d, *J* 14.9, NCH*H*Ar), 6.83-6.89 (2H, m, *Ar*), 7.15-7.18 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.4, 19.9, 31.8, 46.5, 50.9, 52.7, 55.2, 60.9, 114.2, 127.9, 129.6, 159.2, 161.0, 168.0; *m/z* (ESI^+) 313 ($[M+Na]^+$, 83%), 291 (100); HRMS (ESI^+) $C_{16}H_{23}N_2O_3$ ($[M+H]^+$) requires 291.1709; found 291.1707.

(3*R*,6*S*)- and (3*S*,6*S*)-*N*(1),3-Dimethyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one

(3*R*,6*S*)-*trans*-20 and (3*S*,6*S*)-*cis*-21



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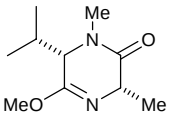


21

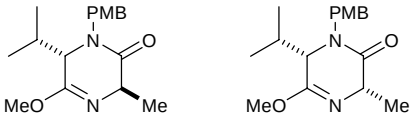
Following *General procedure 2*, BuLi (1.6 M in hexanes, 1.11 mL, 1.77 mmol), **18** (326 mg, 1.77 mmol) and MeI (0.12 mL, 1.95 mmol) in THF (15 mL), gave a 84.5:14.5 mixture of *trans*-**20**:*cis*-**21**. Purification *via* flash column chromatography (eluent Et_2O) gave *trans*-**20** as a colourless oil (200 mg, 57%, >98% de) and *cis*-**21** as a colourless oil (46 mg, 13%, >98% de).

Data for *trans*-**20**: $[\alpha]_D^{23}$ +212 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1696, 1653; δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.91 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.35 (3H, d, *J* 7.3, C(3)*Me*), 2.01-2.11 (1H, m, CH$_3$C*H*CH$_3$), 2.82 (3H, s, N*Me*), 3.65 (3H, s, O*Me*) 3.61 (1H, dd, *J* 4.0, 1.8, C(6)*H*), 3.88 (1H, td, *J* 7.3, 1.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 17.8, 19.4, 20.3, 31.8, 33.7, 52.5, 53.8, 65.9, 159.5, 171.1; *m/z* (ESI^+) 199 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{19}N_2O_2$ ($[M+H]^+$) requires 199.1447; found 199.1446.

Data for *cis*-**21:** $[\alpha]_D^{23}$ +29.6 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1682, 1650; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 1.06 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.45 (3H, d, *J* 7.3, C(3)*Me*), 2.07-2.16 (1H, m, CH$_3$C*H*CH$_3$), 2.93 (3H, s, N*Me*), 3.65 (3H, s, O*Me*), 3.75 (1H, dd, *J* 3.3, 1.9, C(6)*H*), 4.17 (1H, dt, *J* 7.3, 1.9,

C(3)*H*); δ_C (100 MHz, $CDCl_3$) 18.1, 19.8, 21.4, 30.8, 33.7, 52.4, 55.1, 65.2, 158.0, 170.7; *m/*z (ESI^+) 199 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{19}N_2O_2$ ($[M+H]^+$) requires 199.1447; found 199.1448.

(3*R*,6*S*)- and (3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-methyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one (3*R*,6*S*)-*trans*-22 and (3*S*,6*S*)-*cis*-23



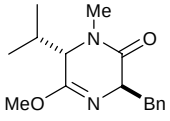
22 **23**

Following *General procedure 2*, BuLi (2.5 M in hexanes, 0.28 mL, 0.70 mmol), **19** (184 mg, 0.63 mmol) and MeI (40 μL, 0.70 mmol) in THF (10 mL), gave a 84:16 mixture of *trans*-**22**:*cis*-**23**. Purification *via* flash column chromatography (eluent 5:2 40-60° petrol:Et_2O) gave *trans*-**22** as a colourless oil (119 mg, 62%, >98% de) and *cis*-**23** as a colourless oil (8 mg, 4%, >98% de).

Data for *trans*-**22**: $[\alpha]_D^{23}$ +22.5 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1694, 1652; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.02 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.54 (3H, d, *J* 7.4, C(3)*Me*), 2.16-2.24 (1H, m, CH$_3$C*H*CH$_3$), 3.64 (3H, s, C(5)O*Me*), 3.67 (1H, dd, *J* 5.9, 1.5, C(6)*H*), 3.79 (3H, s, ArO*Me*), 3.84 (1H, d, *J* 14.8, NC*H*HAr), 4.11 (1H, dq, *J* 7.4, 1.5, C(3)*H*), 5.41 (1H, d, *J* 14.8, NCH*H*Ar), 6.83-6.87 (2H, m, *Ar*), 7.11-7.14 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.7, 20.0, 20.7, 31.5, 46.9, 52.6, 54.0, 55.2, 61.9, 114.1, 128.3, 129.4, 159.1, 159.9, 171.3; *m/*z ($APCI^+$) 305 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}N_2O_3$ ($[M+H]^+$) requires 305.1865; found 305.1862.

Data for *cis*-**23**: ν_{max} (film) 1693, 1654; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.98 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.52 (3H, d, *J* 7.2, C(3)*Me*), 2.11-2.19 (1H, m, CH$_3$C*H*CH$_3$), 3.63 (1H, dd, *J* 4.4, 1.6, C(6)*H*), 3.65 (3H, s, C(5)O*Me*), 3.81 (1H, d, *J* 14.9, NC*H*HAr), 3.81 (3H, s, ArO*Me*), 4.09 (1H, dq, *J* 7.2, 1.6, C(3)*H*), 5.35 (1H, d, *J* 14.9, NCH*H*Ar), 6.79-6.83 (2H, m, *Ar*), 7.09-7.13 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.7, 20.0, 20.7, 31.5, 46.9, 52.6, 55.4, 54.1, 61.7, 114.1, 127.9, 129.8, 156.8, 159.9, 171.2; *m/*z (ESI^+) 305 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}N_2O_3$ ($[M+H]^+$) requires 305.1865; found 305.1853.

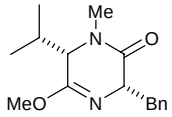
(3*R*,6*S*)-*N*(1)-Methyl-3-benzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one *trans*-24



Following *General procedure 2*, BuLi (1.6 M in hexanes, 1.23 mL, 1.97 mmol), **18** (362 mg, 1.97 mmol) and BnBr (0.26 mL, 2.16 mmol) in THF (15 mL), gave a >99:<1 mixture of *trans*-**24**:*cis*-**25**. Purification

via flash column chromatography (eluent 2:1 hexane:Et_2O) gave *trans*-**24** as a colourless oil (0.44 g, 82%, >98% de); $C_{16}H_{22}N_2O_2$ requires C, 70.0; H, 8.1; N, 10.2%; found C, 69.8; H, 8.4; N, 10.1%; $[\alpha]_D^{22}$ +129.0 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1699, 1652; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.97 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.04-2.16 (1H, m, CH$_3$C*H*CH$_3$), 2.85 (3H, s, N*Me*), 3.12 (1H, dd, *J* 13.3, 7.0, C(3)C*H*H), 3.33 (1H, dd, *J* 13.3, 4.3, C(3)CH*H*), 3.54 (1H, dd, *J* 3.8, 2.0, C(6)*H*), 3.64 (3H, s, O*Me*), 4.20 (1H, ddd, *J* 7.0, 4.3, 2.0, C(3)*H*), 7.11-7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5, 19.4, 31.7, 33.6, 39.6, 52.6, 59.3, 65.4, 126.0, 127.6, 130.3, 138.8, 159.0, 169.6; *m/z* (ESI$^+$) 275 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_2$ ([M+H]$^+$) requires 275.1760; found 275.1760.

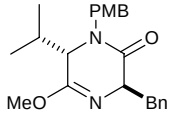
(3*S*,6*S*)-*N*(1)-Methyl-3-benzyl-5-methoxy-6-*iso*-propyl-3,6-dihydro-pyrazine-2-one *cis*-25



BuLi (1.6 M in hexanes, 0.34 mL, 0.55 mmol) was added dropwise to a stirred solution of *trans*-**24** (150 mg, 0.55 mmol) in THF (10 mL) at −78°C. After 45 min, AcOH (47 μL, 0.82 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h. The mixture was diluted with EtOAc (10 mL), washed with H_2O (20 mL), dried, and concentrated *in vacuo* to give a 25:75 mixture of *trans*-**24**:*cis*-**25**. Purification *via* flash column chromatography (eluent 1:2 40-60° petrol:Et_2O) gave *trans*-**24** as a colourless oil (23 mg, 15%, >98% de) and *cis*-**25** as a colourless oil (48 mg, 32%, >98% de).

Data for *cis*-**25**: $[\alpha]_D^{23}$ +7.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1698, 1651; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 1.04 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.95-2.05 (1H, m, CH$_3$C*H*CH$_3$), 2.88 (1H, dd, *J* 13.4, 9.3, C(3)C*H*H), 2.97 (3H, s, N*Me*), 3.39 (1H, dd, *J* 13.4, 3.9, C(3)CH*H*), 3.63 (3H, s, O*Me*), 3.75 (1H, dd, *J* 3.5, 2.3, C(6)*H*), 4.35 (1H, ddd, *J* 9.3, 3.9, 2.3, C(3)*H*), 7.20-7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8, 20.0, 31.0, 34.0, 41.5, 52.5, 60.8, 65.0, 126.3, 128.1, 129.8, 138.7, 158.0, 169.4; *m/z* (ESI$^+$) 275 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_2$ ([M+H]$^+$) requires 275.1760; found 275.1766.

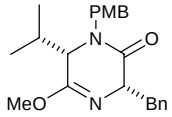
(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one *trans*-26



Following *General procedure 2*, BuLi (1.6 M in hexanes, 6.39 mL, 10.2 mmol), **19** (2.70 g, 9.29 mmol), and BnBr (1.22 mL, 10.2 mmol) in THF (120 mL), gave a >99:<1 mixture of *trans*-**26**:*cis*-**27**. Purification *via*

flash column chromatography (eluent 7:3 40-60° petrol:EtOAc) gave *trans*-**26** as a colourless oil (3.29 g, 94%, >98% de); $[\alpha]_D^{22}$ +3.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1648; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.98 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.12-2.20 (1H, m, CH$_3$C*H*CH$_3$), 3.37-3.39 (2H, m, C(3)C*H*$_2$), 3.50 (1H, dd, *J* 5.0, 1.3, C(6)*H*), 3.68 (3H, s, C(5)O*Me*), 3.72 (1H, d, *J* 15.2, NC*H*HAr), 3.77 (3H, s, ArO*Me*), 4.40 (1H, td, *J* 4.6, 1.3, C(3)*H*), 5.44 (1H, d, *J* 15.2, NCH*H*Ar), 6.72-6.76 (4H, m, *Ar*), 7.26-7.28 (3H, m, *Ph*), 7.35-7.37 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3, 19.8, 31.3, 39.6, 46.1, 52.5, 55.2, 59.3, 60.9, 114.1, 126.1, 127.7, 129.1, 130.7, 127.3, 138.4, 158.9, 159.1, 160.3; *m/*z (ESI$^+$) 381 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{29}N_2O_3$ ([M+H]$^+$) requires 381.2178; found 381.2180.

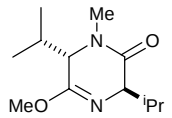
(3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one *cis*-27



BuLi (1.6 M in hexanes, 0.33 mL, 0.52 mmol) was added dropwise to a stirred solution of *trans*-**26** (198 mg, 0.52 mmol) in THF (20 mL) at −78°C. After 45 min, AcOH (45 μL, 0.78 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h. The mixture was diluted with EtOAc (10 mL), washed with H_2O (20 mL), dried, and concentrated *in vacuo* to give a 25:75 mixture of *trans*-**26**:*cis*-**27**. Purification *via* flash column chromatography (eluent 7:3 hexane:Et_2O) gave *trans*-**26** as a colourless oil (47 mg, 24%, >98% de) and *cis*-**27** as a colourless oil (115 mg, 58%, >98% de).

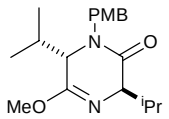
Data for *cis*-**27**: $[\alpha]_D^{23}$ +7.5 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1696, 1651; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.05 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.01-2.10 (1H, m, CH$_3$C*H*CH$_3$), 2.96 (1H, dd, *J* 13.2, 9.5, C(3)C*H*H), 3.45 (1H, dd, *J* 13.2, 4.1, C(3)CH*H*), 3.59 (3H, s, C(5)O*Me*), 3.77 (1H, dd, *J* 4.3, 2.0, C(6)*H*), 3.80 (3H, s, ArO*Me*), 3.90 (1H, d, *J* 14.9, NC*H*HAr), 4.44 (1H, ddd, *J* 9.5, 4.1, 2.0, C(3)*H*), 5.43 (1H, d, *J* 14.9, NCH*H*Ar), 6.86-6.88, (2H, m, *Ar*), 7.16-7.18 (2H, m, *Ar*), 7.30-7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.4, 20.5, 30.3, 41.7, 46.5, 52.4, 55.2, 60.7, 61.1, 114.1, 126.3, 128.1, 129.7, 129.8, 128.0, 138.8, 158.0, 159.2, 169.3; *m/*z (ESI$^+$) 403 ([M+Na]$^+$, 20%), 381 (100); HRMS (ESI$^+$) $C_{23}H_{29}N_2O_3$ ([M+H]$^+$) requires 381.2178; found 381.2168.

(6*S*,3*R*)-*N*(1)-Methyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one *trans*-28



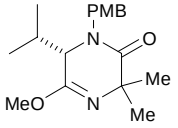
Following *General procedure 2*, BuLi (1.6 M in hexanes, 2.54 mL, 4.07 mmol), **18** (750 mg, 4.07 mmol), and ^{i}PrI (0.55 mL, 4.48 mmol) in THF (50 mL), gave a 94:6 mixture of *trans*-**28**:*cis*-**29**. Purification *via* flash column chromatography (eluent 1:1 30-40° petrol:Et_2O) gave *trans*-**28** as a pale yellow crystalline solid (892 mg, 84%, >98% de); mp 58-59°C; $[\alpha]_D^{22}$ +208 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1698, 1646; δ_H (400 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.88 (3H, d, *J* 7.2, C(6)CH*Me*Me), 1.04 (3H, d, *J* 7.2, C(6)CHMe*Me*), 1.11 (3H, d, *J* 6.8, C(3)CHMe*Me*), 2.15-2.24 (1H, m, C(6)C*H*Me_2), 2.60-2.69 (1H, m, C(3)C*H*Me_2), 2.96 (3H, s, N*Me*), 3.71 (3H, s, O*Me*), 3.75 (1H, dd, *J* 3.4, 2.0, C(6)*H*), 3.82 (1H, dd, *J* 2.4, 2.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 16.1, 19.8, 17.4, 19.3, 30.6, 31.7, 33.4, 52.2, 62.5, 65.2, 159.0, 170.3; *m/z* (ESI^+) 249 ($[M+Na]^+$, 70%); HRMS (ESI^+) $C_{12}H_{23}N_2O_2$ ($[M+H]^+$) requires 227.1760; found 227.1750.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one *trans*-30



Following *General procedure 2*, BuLi (1.6 M in hexanes, 0.33 mL, 0.52 mmol), **19** (151 mg, 0.52 mmol) and ^{i}PrI (57.2 μL, 0.57 mmol) in THF (10 mL), gave a 97.5:2.5 mixture of *trans*-**30**:*cis*-**31**. Purification *via* flash column chromatography (eluent 2:1 pentane:Et_2O) gave *trans*-**30** as a colourless oil (108 mg, 62%, >98% de); $C_{19}H_{28}N_2O_3$ requires C, 68.7; H, 8.5; N, 8.4%; found C, 68.4; H, 8.6; N, 8.3%; $[\alpha]_D^{23}$ +39.3 (*c* 1.10 in $CHCl_3$); ν_{max} (film) 1704, 1651; δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.6, C(3)CH*Me*Me), 0.87 (3H, d, *J* 7.1, C(6)CH*Me*Me), 1.00 (3H, d, *J* 7.1, C(6)CHMe*Me*), 1.12 (3H, d, *J* 7.1, C(3)CHMe*Me*), 2.15-2.24 (1H, m, C(6)C*H*Me_2), 2.65-2.76 (1H, m, C(3)C*H*Me_2), 3.65 (3H, s, C(5)O*Me*), 3.67 (1H, dd, *J* 3.5, 1.8, C(6)*H*), 3.77 (3H, s, ArO*Me*), 3.77 (1H, d, *J* 14.8, NC*H*HAr), 3.88 (1H, dd, *J* 2.8, 1.8, C(3)*H*), 5.48 (1H, d, *J* 14.8, NCH*H*Ar), 6.81-6.86 (2H, m, *Ar*), 7.09-7.14 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2, 17.3, 19.9, 20.0, 30.8, 31.4, 46.2, 52.3, 55.2, 60.8, 62.6, 114.1, 128.4, 129.4, 159.1, 159.2, 170.2; *m/z* (ESI^+) 333 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}N_2O_3$ ($[M+H]^+$) requires 333.2178; found 333.2177.

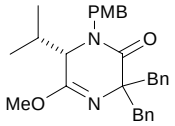
(*S*)-*N*(1)-*p*-Methoxybenzyl-3,3-dimethyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 32



Following *General procedure 2*, BuLi (2.5 M in hexanes, 0.23 mL, 0.57 mmol), *trans*-**22** (174 mg, 0.57 mmol) and MeI (32 μL, 0.63 mmol) in THF (10 mL) gave, after purification *via* flash column

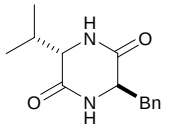
chromatography (eluent 2:1 30-40° petrol:Et_2O), **32** as a colourless oil (115 mg, 63%); $[\alpha]_D^{22}$ −8.5 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1702, 1634; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.04 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.47 (3H, s, C(3)*Me*$_A$), 1.49 (3H, s, C(3)*Me*$_B$), 2.14-2.22 (1H, m, CH$_3$C*H*CH$_3$), 3.61 (3H, s, C(5)O*Me*), 3.72 (1H, d, *J* 2.8, C(6)*H*), 3.80 (3H, s, ArO*Me*), 3.80 (1H, d, *J* 14.7, NC*H*HAr), 5.46 (1H, d, *J* 14.7, NCH*H*Ar), 6.84-6.88 (2H, m, *Ar*), 7.11-7.16 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.5, 20.4, 29.1, 31.6, 29.9, 45.9, 52.0, 55.2, 57.9, 61.0, 114.1, 128.3, 129.4, 155.7, 159.1, 173.4; *m/*z (ESI$^+$) 319 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{27}N_2O_3$ ([M+H]$^+$) requires 319.2022; found 319.2024.

(*S*)-*N*(1)-*p*-Methoxybenzyl-3,3-dibenzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 33



Following *General procedure 2*, BuLi (1.6 M in hexanes, 0.24 mL, 0.38 mmol), *trans*-**26** (133 mg, 0.35 mmol) and BnBr (46 μL, 0.38 mmol) in THF (10 mL) gave, after purification *via* flash column chromatography (eluent 2:1 hexane:Et_2O), **33** as a yellow oil (129 mg, 79%); $[\alpha]_D^{23}$ −33.3 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1643; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.75 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.64-1.73 (1H, m, CH$_3$C*H*CH$_3$), 2.93 (1H, d, *J* 12.6, C(3)C*H*$_A$H$_B$Ph), 3.01 (1H, d, *J* 2.2, C(6)*H*), 3.22 (1H, d, *J* 12.6, C(3)C*H*$_C$H$_D$Ph), 3.47 (1H, d, *J* 12.6, C(3)CH$_C$*H*$_D$Ph), 3.56 (1H, d, *J* 12.6, C(3)CH$_A$*H*$_B$Ph), 3.78 (6H, app s, C(5)O*Me*, ArO*Me*), 3.97 (1H, d, *J* 14.8, NC*H*HAr), 4.84 (1H, d, *J* 14.8, NCH*H*Ar), 6.52-6.54 (2H, m, *Ar*), 6.69-6.71 (2H, m, *Ar*), 7.17-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9, 20.4, 29.0, 46.8, 46.9, 47.9, 52.1, 55.1, 60.7, 66.6, 113.7, 126.4, 126.5, 127.8 (2C), 127.9, 129.3, 130.7, 131.4, 127.5, 137.3, 157.3, 158.7, 169.8; *m/*z (APCI$^+$) 471 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}N_2O_3$ ([M+H]$^+$) requires 471.2648; found 471.2646.

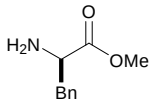
(3*S*,6*R*)-3-*iso*-Propyl-6-benzyl-piperazine-2,5-dione 34



Following *General Procedure 3*, **26** (1.45 g, 3.81 mmol) and TFA (50 mL) gave **34** as an off white solid (676 mg, 72%); mp 256-257°C; $[\alpha]_D^{23}$ −58.3 (*c* 1.0 in AcOH); ν_{max} (KBr) 3193, 1670; δ_H (400 MHz, DMSO-d_6) 0.75 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.82 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.99-2.08 (1H, m, CH$_3$C*H*CH$_3$), 2.87

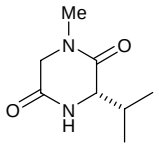
(1H, dd, *J* 13.6, 4.9, C(6)C*H*HPh), 2.95 (1H, dd, *J* 2.5, 2.0, C(3)*H*), 3.15 (1H, dd, *J* 13.6, 3.8, C(6)CH*H*Ph), 4.17 (1H, ddd, *J* 4.9, 3.8, 2.0, C(6)*H*), 7.18-7.28 (5H, m, *Ph*), 7.96 (1H, app br s, N(4)*H*), 8.15 (1H, app br s, N(1)*H*); δ_C (100 MHz, DMSO-d_6) 17.4, 19.0, 32.4, 38.8, 56.0, 59.8, 127.5, 128.8, 131.0, 136.9, 167.9, 168.2; *m/*z (ESI$^+$) 247 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}N_2O_2$ ([M+H]$^+$) requires 247.1447; found 247.1437.

(*R*)-Phenylalanine methyl ester 38



Following *General Procedure 4*, **34** (275 mg, 1.11 mmol) and conc HCl (30 mL) gave a mixture of amino acid hydrochloride salts **35** and **36** (447 mg); δ_H (400 MHz, MeOD) 1.11 (6H, d, *J* 7.2, C*H*$_3$CHC*H*$_3$), 2.28-2.40 (1H, m, CH$_3$C*H*CH$_3$), 3.23 (1H, dd, *J* 14.5, 7.2, C*H*HPh), 3.33 (1H, dd, *J* 14.5, 5.8, CH*H*Ph), 3.89 (1H, d, *J* 4.1, ^{i}PrC*H*), 4.29 (1H, app t, *J* 6.5, C*H*CH$_2$Ph), 7.31-7.41 (5H, m, *Ph*). Subsequently, following *General Procedure 5*, the mixture of amino acid salts **35** and **36**, $SOCl_2$ (0.28 mL, 2.26 mmol) and MeOH (40 mL) gave a mixture of methyl ester hydrochloride salts which was neutralized and distilled as outlined in *General Procedure 5*, to give **38** as a colourless oil (142 mg, 74%); $[\alpha]_D^{23}$ –32.2 (*c* 1.0 in EtOH) for **38**.HCl; {lit.[2] $[\alpha]_D^{25}$ –37.0 (*c* 2.0 in EtOH) for **38**.HCl}; ν_{max} (film) 3378, 1738; δ_H (400 MHz, $CDCl_3$) 1.51 (2H, br s, N*H*$_2$), 2.84 (1H, dd, *J* 13.6, 7.9, C*H*HPh), 3.07 (1H, dd, *J* 13.6, 5.1, CH*H*Ph), 3.68 (3H, s, O*Me*), 3.71 (1H, m, C*H*), 7.15-7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 41.1, 51.9, 55.8, 126.8, 128.5, 129.2, 137.2, 175.4; *m/*z (ESI$^+$) 180 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{14}NO_2$ ([M+H]$^+$) requires 180.1025; found 180.1020.

(*S*)-*N*(1)-Methyl-3-*iso*-propyl-piperazine-2,5-dione 45



CAN (8.61 g, 15.7 mmol) was added to (*S*)-*N*(1)-methyl-*N*(4)-*p*-methoxybenzyl-3-*iso*-propyl-diketopiperazin-2,5-dione (1.52 g, 5.23 mmol) in a solution of MeCN/H_2O (3:1, 160 mL) and stirred at rt for 16 h. The reaction was then quenched with sat aq K_2CO_3. H_2O (100 mL) was then added followed by an organic wash with Et_2O. The product was extracted from the organic layer with two portions of H_2O. The aqueous layers were combined and concentrated *in vacuo*. Trituration with DCM followed by concentration of the organic solution *in vacuo* gave **45** (513 g, 58%) as a white crystalline solid; Found C, 56.3; H, 8.3; N, 16.5. $C_8H_{14}N_2O_2$ requires C, 56.5; H, 8.3; N, 16.5%; mp 135-136°C; $[\alpha]_D^{23}$ –3.6 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 3392, 1683, 1651; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 1.00 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.33-2.40 (1H, m, CH$_3$C*H*CH$_3$), 2.95 (3H, s, N*Me*), 3.85 (1H, d, *J* 17.9, C(6)*H*H), 3.86 (1H, d, *J* 3.0, C(3)*H*), 4.01 (1H, d, *J* 17.9, C(6)H*H*), 7.80 (1H, app br s, N*H*); δ_C (100 MHz, $CDCl_3$) 16.2, 18.7, 33.1, 33.7, 51.3,

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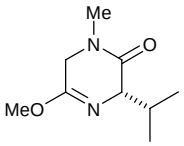
[2] S.-T. Chen, K.-T. Wang and C.-H. Wong, *J. Chem. Soc., Chem. Commun.*, **1986**, 1514.

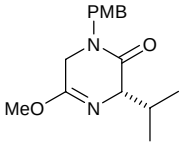
60.6, 165.8, 166.3; *m/*z (ESI$^-$) 169 ([M−H]$^-$, 100%); HRMS (ESI$^-$) $C_8H_{13}N_2O_2$ ([M−H]$^-$) requires 169.0977; found 169.0966.

(*S*)-*N*(1)-Methyl-3-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 47



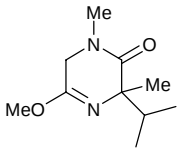
Following *General Procedure 1*, **45** (492 mg, 2.89 mmol), Me_3OBF_4 (860 mg, 5.78 mmol) and $BmimBF_4$ (10 mL) gave **47** as a colourless oil (442 mg, 83%); $[\alpha]_D^{23}$ −19.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1711, 1651; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.08 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.40-2.48 (1H, m, CH$_3$C*H*CH$_3$), 2.96 (3H, s, N*Me*), 3.73 (3H, s, O*Me*), 3.83 (1H, dd, *J* 16.9, 2.5, C(6)*H*H), 3.86 (1H, dd, *J* 16.9, 2.3, C(6)H*H*), 4.01 (1H, ddd, *J* 3.3, 2.5, 2.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 16.6, 17.9, 33.0, 33.4, 48.3, 52.7, 63.9, 156.5, 169.1; *m/*z (ESI$^+$) 207 ([M+Na]$^+$, 40%), 185 (100); HRMS (ESI$^+$) $C_9H_{17}N_2O_2$ ([M+H]$^+$) requires 185.1290; found 185.1284.

(*S*)-*N*(1)-*p*-Methoxybenzyl-3-*iso*-propyl-5-methoxy-3,6-dihydro-pyrazine-2-one 48



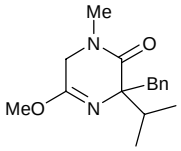
Following *General Procedure 1*, **46** (425 mg, 1.53 mmol), Me_3OBF_4 (455 mg, 3.07 mmol) and $BmimBF_4$ (5 mL) gave, after flash column chromatography (eluent Et_2O), **48** as a white crystaline solid (275 mg, 62%); $C_{16}H_{22}N_2O_3$ requires C, 66.2; H, 7.6; N, 9.7%; found C, 66.3; H, 7.6; N, 9.5%; mp 67-68°C (DCM-heptane); $[\alpha]_D^{24}$ +1.6 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 1640; δ_H (400 MHz, C_6D_6) 0.92 (3H, d, *J* 7.2, C*H*$_3$CHCH$_3$), 1.24 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 2.81-2.88 (1H, m, CH$_3$C*H*CH$_3$), 3.42 (3H, s, C(5)O*Me*), 3.46 (1H, dd, *J* 17.1, 2.8, C(6)*H*H), 3.55 (3H, s, ArO*Me*), 3.58 (1H, dd, *J* 17.1, 2.8, C(6)H*H*), 4.13 (1H, d, *J* 14.3, NC*H*HAr), 4.21 (1H, app dd, *J* 5.8, 2.8, C(3)*H*), 4.76 (1H, d, *J* 14.3, NCH*H*Ar), 6.80 (2H, m, *Ar*), 7.19 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.6, 19.5, 33.0, 45.2, 48.5, 52.6, 55.1, 64.1, 114.1, 127.8, 129.8, 156.9, 159.3, 168.6; *m/*z (APCI$^+$) 291 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_3$ ([M+H]$^+$) requires 291.1709; found 291.1707.

(*RS*)-*N*(1),3-Dimethyl-3-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 49



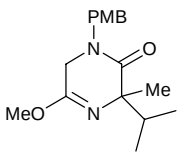
Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.41 mL, 0.63 mmol), **47** (105 mg, 0.57 mmol), THF (10 mL) and MeI (40 μL, 0.57 mmol) gave, after flash column chromatography (eluent 1:1 pentane:Et_2O), **49** as a colourless oil (81 mg, 72%); $[\alpha]_D^{23}$ −1.22 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 1708, 1652; δ_H (400 MHz, $CDCl_3$) 0.72 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.96 (3H, d, *J* 7.2, CH$_3$CHC*H*$_3$), 1.34 (3H, s, C(3)*Me*), 2.19-2.29 (1H, m, CH$_3$C*H*CH$_3$), 2.95 (3H, s, N*Me*), 3.70 (3H, s, *OMe*), 3.89 (2H, app s, C(6)*H*$_2$); δ_C (100 MHz, $CDCl_3$) 15.7, 18.1, 26.0, 33.5, 36.8, 48.4, 52.5, 63.3, 154.5, 169.3; *m/*z (ESI$^+$) 199 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{19}N_2O_2$ ([M+H]$^+$) requires 199.1447; found 199.1452.

(*RS*)-*N*(1)-Methyl-3-benzyl-3-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 50



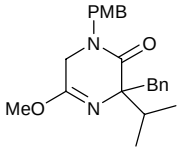
Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.53 mL, 0.82 mmol), **47** (150 mg, 0.82 mmol), THF (10 mL) and BnBr (0.11 mL, 0.90 mmol) gave, after flash column chromatography (eluent 2:1 40-60° petrol:Et_2O), **50** (143 mg, 64%) as a colourless oil; $[\alpha]_D^{23}$ −0.21 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1708, 1654; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.10 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.43 (1H, d, *J* 16.5, C(6)*H*H), 2.49-2.59 (1H, m, CH$_3$C*H*CH$_3$), 2.63 (3H, s, N*Me*), 2.87 (1H, d, *J* 12.4, C(3)C*H*HPh), 3.09 (1H, d, *J* 12.4, C(3)CH*H*Ph), 3.34 (1H, d, *J* 16.5, C(6)H*H*), 3.74 (3H, s, O*Me*), 7.02-7.06 (2H, m, *Ph*), 7.14-7.21 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9, 18.8, 33.0, 35.4, 44.5, 47.7, 52.5, 62.8, 126.4, 127.6, 130.4, 137.4, 156.0, 170.8; *m/*z (ESI$^+$) 275 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_2$ ([M+H]$^+$) requires 275.1760; found 275.1763.

(*RS*)-*N*(1)-*p*-Methoxybenzyl-3-methyl-3-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 51



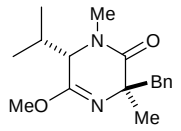
Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.33 mL, 0.52 mmol), **48** (138 mg, 0.475 mmol), THF (10 mL) and MeI (33 μL, 0.52 mmol) gave, after flash column chromatography (eluent 2:1 40-60° petrol:Et_2O), **51** (117 mg, 81%) as a colourless oil; $[\alpha]_D^{22}$ +0.7 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1650; δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.6, C*H*$_3$CHCH$_3$), 0.96 (3H, d, *J* 6.6, CH$_3$CHC*H*$_3$), 1.37 (3H, s, C(3)*Me*), 2.25-2.35 (1H, m, CH$_3$C*H*CH$_3$), 3.65 (3H, s, C(5)O*Me*), 3.73 (2H, app s, C(6)*H*$_2$), 3.78 (3H, s, ArO*Me*), 4.42 (1H, d, *J* 14.1, NC*H*HAr), 4.64 (1H, d, *J* 14.1, NCH*H*Ar), 6.82-6.87 (2H, m, *Ar*), 7.17-7.22 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.8, 18.1, 26.1, 36.7, 45.3, 48.6, 52.5, 55.2, 63.4, 114.0, 128.1, 129.8, 154.9, 159.2, 172.1; *m/*z (APCI$^+$) 305 ([M+H]$^+$, 50%); HRMS (ESI$^+$) $C_{17}H_{25}N_2O_3$ ([M+H]$^+$) requires 305.1865; found 305.1864.

(*RS*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 52



Following *General Procedure 2*, BuLi (0.13 mL, 1.6 M, 0.21 mmol), **48** (56 mg, 0.193 mmol), THF (10 mL) and BnBr (25 μL, 0.21 mmol) gave, after flash column chromatography (eluent 3:1 40-60° petrol:EtOAc), **52** (47 mg, 64%) as a yellow oil; $[\alpha]_D^{22}$ −2.5 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1651; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 6.7, C*H*$_3$CHCH$_3$), 1.12 (3H, d, *J* 6.7, CH$_3$CHC*H*$_3$), 2.53-2.63 (1H, m, CH$_3$C*H*CH$_3$), 2.56 (1H, d, *J* 16.7, C(6)*H*H), 2.95 (1H, d, *J* 12.2, C(3)C*H*HPh), 3.18 (1H, d, *J* 12.2, C(3)CH*H*Ph), 3.30 (1H, d, *J* 16.7, C(6)H*H*), 3.72 (3H, s, C(5)O*Me*), 3.77 (3H, s, ArO*Me*), 4.00 (1H, d, *J* 14.9, NC*H*HAr), 4.56 (1H, d, *J* 14.9, NCH*H*Ar), 6.74-6.79 (2H, m, *Ar*), 6.88-6.94 (2H, m, *Ar*), 7.05-7.22 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.0, 18.7, 36.3, 44.4, 44.7, 48.2, 52.5, 55.2, 68.4, 113.9, 126.3, 127.6, 129.5, 130.9, 127.8, 137.5, 156.1, 159.0, 170.2; *m/*z (APCI$^+$) 381 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{29}N_2O_3$ ([M+H]$^+$) requires 381.2178; found 381.2176.

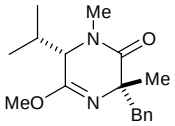
(3*R*,6*S*)-*N*(1),3-Dimethyl-3-benzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 53



Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.44 mL, 0.70 mmol), **20** (138 mg, 0.70 mmol), THF (10 mL) and BnBr (91 μL, 0.77 mmol) gave a 99:1 mixture of **53**:**54**. Purification *via* flash column chromatography (eluent 1:1 40-60° petrol:Et_2O) gave **53** as a colourless oil (155 mg, 81%, >98% de); $[\alpha]_D^{23}$

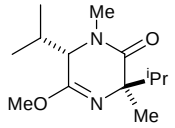
+75.0 (*c* 1.15 in $CHCl_3$); ν_{max} (film) 1699, 1650; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.94 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.53 (3H, s, C(3)*Me*), 1.92-2.03 (1H, m, CH$_3$C*H*CH$_3$), 2.66 (3H, s, N*Me*), 2.75 (1H, d, *J* 12.4, C(3)C*H*HPh), 3.19 (1H, d, *J* 2.5, C(6)*H*), 3.30 (1H, d, *J* 12.4, C(3)CH*H*Ph), 3.66 (3H, s, O*Me*), 7.05-7.17 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2, 19.5, 28.3, 30.2, 33.2, 48.8, 52.1, 62.0, 64.7, 126.2, 127.3, 130.2, 137.4, 155.9, 171.4; *m/*z (ESI^+) 289 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}N_2O_2$ ($[M+H]^+$) requires 289.1916; found 289.1918.

(3*S*,6*S*)-*N*(1),3-Dimethyl-3-benzyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 54



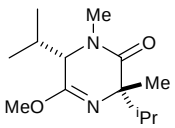
Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.28 mL, 0.44 mmol), **24** (121 mg, 0.44 mmol), THF (10 mL) and MeI (30 μL, 0.49 mmol) gave a 3.5:96.5 mixture of **53**:**54**. Purification *via* flash column chromatography (eluent 1:1 40-60° petrol:Et_2O) gave **54** as a colourless oil (63 mg, 50%, >98% de); $[\alpha]_D^{23}$ +77.8 (*c* 2.8 in $CHCl_3$); ν_{max} (film) 1696, 1637; δ_H (400 MHz, $CDCl_3$) 0.33 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 0.87 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.40 (3H, s, C(3)*Me*), 1.80-1.91 (1H, m, CH$_3$C*H*CH$_3$), 2.88 (3H, s, N*Me*), 2.95 (1H, d, *J* 12.0, C(3)C*H*HPh), 3.27 (1H, d, *J* 12.0, C(3)CH*H*Ph), 3.66 (3H, s, O*Me*), 3.73 (1H, d, *J* 3.0, C(6)*H*), 7.12-7.22 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3, 19.8, 30.2, 30.5, 33.9, 46.5, 52.1, 61.7, 64.9, 126.3, 127.7, 131.1, 137.6, 155.7, 172.2; *m/z* (ESI^+) 289 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}N_2O_2$ ($[M+H]^+$) requires 289.1916; found 289.1920.

(3*R*,6*S*)-*N*(1),3-Dimethyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydro-pyrazine-2-one 55



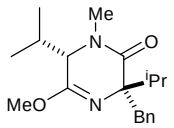
Following *General Procedure 2*, BuLi (2.5 M in hexanes, 1.11 mL, 2.78 mmol), **20** (551 mg, 2.78 mmol), THF (20 mL) and ^{i}PrI (0.31 mL, 3.06 mmol) gave a >99:<1 mixture of **55**:**56**. Purification *via* flash column chromatography (eluent 1:1 30-40° petrol:Et_2O) gave **55** as a colourless oil (548 mg, 82%, >98% de); $[\alpha]_D^{22}$ +135.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1704, 1650; δ_H (400 MHz, $CDCl_3$) 0.60 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.86 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.95 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.07 (3H, d, *J* 7.2, C(6)CHMe*Me*), 1.35 (3H, s, C(3)*Me*), 2.10-2.20 (1H, m, C(6)C*H*Me$_2$), 2.20-2.29 (1H, m, C(3)C*H*Me$_2$), 2.90 (3H, s, N*Me*), 3.65 (3H, s, O*Me*), 3.80 (1H, d, *J* 2.7, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 15.5, 17.4, 17.8, 19.7, 26.0, 30.4, 33.2, 37.2, 51.9, 62.3, 64.8, 155.8, 173.3; *m/z* (ESI^+) 253 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{25}N_2O_2$ ($[M+H]^+$) requires 241.1916; found 241.1917.

(3*S*,6*S*)-*N*(1),3-Dimethyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 56



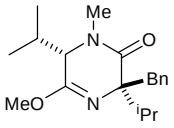
Following *General Procedure 2*, BuLi (2.5 M in hexanes, 0.86 mL, 2.18 mmol), **28** (492 mg, 2.18 mmol), THF (20 mL) and MeI (0.13 mL, 2.40 mmol) gave a 1:99 mixture of **55**:**56**. Purification *via* flash column chromatography (eluent 1:1 30-40° petrol:Et_2O) gave **56** as a pale yellow oil (471 mg, 90%, >98% de); $[\alpha]_D^{22}$ +102.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1701, 1644; δ_H (400 MHz, $CDCl_3$) 0.73 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.82 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.93 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.06 (3H, d, *J* 7.2, C(6)CHMe*Me*), 1.29 (3H, s, C(3)*Me*) 2.10-2.21 (2H, m, 2 × C*H*Me_2), 2.87 (3H, s, N*Me*), 3.58 (3H, s, O*Me*), 3.77 (1H, d, *J* 2.7, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 16.2, 17.4, 19.1, 20.3, 27.2, 30.5, 33.7, 35.5, 51.8, 62.6, 64.7, 155.6, 173.2; *m/z* (ESI^+) 263 ($[M+Na]^+$, 70%), 241 (100); HRMS (ESI^+) $C_{13}H_{25}N_2O_2$ ($[M+H]^+$) requires 241.1916; found 241.1908.

(3*R*,6*S*)-*N*(1)-Methyl-3-benzyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 57



Following *General Procedure 2*, BuLi (2.5 M in hexanes, 0.89 mL, 2.23 mmol), **24** (610 mg, 2.23 mmol), THF (20 mL) and ^{i}PrI (0.22 mL, 2.45 mmol) gave a >99:<1 mixture of **57**:**58**. Purification *via* flash column chromatography (eluent 3:2 30-40° petrol:Et_2O) gave **57** as a colourless oil (660 mg, 94%, >98% de); $[\alpha]_D^{22}$ +106.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1698, 1644; δ_H (400 MHz, $CDCl_3$) –0.07 (3H, d, *J* 7.2, C(6)CH*Me*Me), 0.71 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.74 (3H, d, *J* 7.2, C(6)CHMe*Me*), 1.03 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.65-1.73 (1H, m, C(6)C*H*Me_2), 2.25-2.35 (1H, m, C(3)C*H*Me_2), 2.81 (3H, s, N*Me*), 2.96 (1H, d, *J* 12.3, C(3)C*H*HPh), 3.35 (1H, d, *J* 12.3, C(3)CH*H*Ph), 3.61 (1H, d, *J* 2.4, C(6)*H*), 3.71 (3H, s, O*Me*), 7.06-7.19 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2, 16.2, 17.7, 19.5, 30.1, 33.1, 38.9, 43.0, 51.9, 64.3, 67.6, 126.0, 127.6, 131.1, 138.1, 156.5, 170.9; *m/z* (ESI^+) 317 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}N_2O_2$ ($[M+H]^+$) requires 317.2229; found 317.2235.

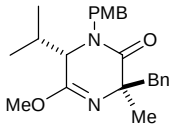
(3*S*,6*S*)-*N*(1)-Methyl-3-benzyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 58



Following *General Procedure 2*, BuLi (2.5 M in hexanes, 1.00 mL, 2.51 mmol), **28** (568 mg, 2.51 mmol), THF (20 mL) and benzylbromide (0.30 mL, 2.76 mmol) gave a <1:>99 mixture of **57**:**58**. Purification *via*

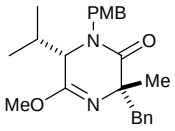
flash column chromatography (eluent 1:1 30-40° petrol:Et_2O) gave **58** as a colourless oil (592 mg, 75%, >98% de); $[\alpha]_D^{22}$ +26.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1704, 1651; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.81 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.95 (3H, d, *J* 7.2, C(6)CHMe*Me*), 1.12 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.91-2.02 (1H, m, C(6)C*H*Me_2), 2.50-2.58 (1H, m, C(3)C*H*Me_2), 2.54 (3H, s, N*Me*), 2.60 (1H, d, *J* 2.0, C(6)*H*), 2.87 (1H, d, *J* 12.3, C(3)C*H*HPh), 3.02 (1H, d, *J* 12.3, C(3)CH*H*Ph), 3.74 (3H, s, O*Me*), 6.98-7.02 (2H, m, *Ph*), 7.17-7.21 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9, 16.6, 19.7, 19.9, 29.7, 32.8, 34.9, 45.8, 51.8, 63.7, 67.8, 126.2, 127.3, 130.1, 137.3, 156.9, 170.9; *m/z* (ESI^+) 317 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}N_2O_2$ ($[M+H]^+$) requires 317.2229; found 317.2225.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3-methyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 59



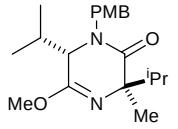
Following *General Procedure 2*, BuLi (2.5 M in hexanes, 0.21 mL, 0.53 mmol), **22** (162 mg, 0.53 mmol), THF (10 mL) and BnBr (70 μL, 0.59 mmol) gave a 99:1 mixture of **59**:**60**. Purification *via* flash column chromatography (eluent 3:1 hexane:Et_2O) gave **59** as a colourless oil (164 mg, 78%, >98% de); $C_{24}H_{30}N_2O_3$ requires C, 73.1; H, 7.7; N, 7.1%; found C, 72.9; H, 7.7; N, 7.1%; $[\alpha]_D^{22}$ –53.1 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 1651; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.89 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.63 (3H, s, C(3)*Me*), 1.98-2.09 (1H, m, CH$_3$C*H*CH$_3$), 2.90 (1H, d, *J* 12.7, C(3)C*H*HPh), 3.26 (1H, d, *J* 2.8, C(6)*H*), 3.42 (1H, d, *J* 12.7, C(3)CH*H*Ph), 3.63 (1H, d, *J* 15.0, NC*H*HAr), 3.70 (3H, s, C(5)O*Me*), 3.75 (3H, s, ArO*Me*), 5.38 (1H, d, *J* 15.0, NCH*H*Ar), 6.44-6.47 (2H, m, *Ar*), 6.64-6.67 (2H, m, *Ar*), 7.20-7.28 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 20.1, 28.9, 29.4, 45.1, 48.7, 52.1, 55.1, 59.6, 62.4, 113.9, 126.2, 126.9, 127.8, 129.4, 130.8, 137.7, 156.5, 158.8, 171.0; *m/z* (ESI^+) 395 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{31}N_2O_3$ ($[M+H]^+$) requires 395.2335; found 395.2328.

(3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3-methyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 60



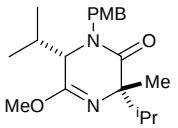
Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.28 mL, 0.45 mmol), **26** (158 mg, 0.45 mmol), THF (10 mL) and MeI (28 μL, 0.45 mmol) gave a 2:98 mixture of **59**:**60**. Purification *via* flash column chromatography (eluent 3:1 hexane:Et_2O) gave **60** as a colourless oil (112 mg, 68%, >98% de); $[\alpha]_D^{23}$ −17.0 (*c* 0.95 in $CHCl_3$); ν_{max} (film) 1644; δ_H (400 MHz, $CDCl_3$) 0.26 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.89 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.43 (3H, s, C(3)*Me*), 1.85-1.95 (1H, m, CH$_3$C*H*CH$_3$), 3.02 (1H, d, *J* 12.9, C(3)C*H*HPh), 3.35 (1H, d, *J* 12.9, C(3)CH*H*Ph), 3.63 (3H, s, C(5)O*Me*), 3.64 (1H, d, *J* 3.2, C(6)*H*), 3.80 (3H, s, ArOC*H*$_3$), 3.83 (1H, d, *J* 14.0, NC*H*HAr), 5.41 (1H, d, *J* 14.0, NCH*H*Ar), 6.82-6.88 (2H, m, *Ar*), 7.08-7.16 (2H, m, *Ar*), 7.18-7.27 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8, 20.4, 29.7, 30.8, 46.2, 46.4, 52.0, 55.2, 60.7, 61.9, 114.1, 126.4, 127.7, 129.4, 131.2, 128.3, 137.6, 155.9, 159.0, 172.1; *m/*z (ESI$^+$) 417 ([M+Na]$^+$, 100%), 395 (35); HRMS (ESI$^+$) $C_{24}H_{31}N_2O_3$ ([M+H]$^+$) requires 395.2335; found 395.2333.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3,6-di-*iso*-propyl-3-methyl-5-methoxy-3,6-dihydropyrazine-2-one 61



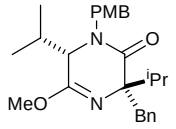
Following *General Procedure 2*, BuLi (2.5 M in hexanes, 0.15 mL, 0.37 mmol), **22** (114 mg, 0.37 mmol), THF (10 mL) and ^{i}PrI (40 μL, 0.41 mmol) gave a 99:1 mixture of **61**:**62**. Purification *via* flash column chromatography (eluent 3:1 30-40° petrol:Et_2O) gave **61** as a colourless oil (93 mg, 72%, >98% de); $[\alpha]_D^{23}$ −14.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1705, 1646; δ_H (400 MHz, $CDCl_3$) 0.62 (3H, d, *J* 6.6, C(3)CH*Me*Me), 0.85 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.97 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.03 (3H, d, *J* 7.1, C(6)CHMe*Me*), 1.41 (3H, s, C(3)*Me*), 2.14-2.25 (1H, m, C(6)C*H*Me$_2$), 2.25-2.38 (1H, m, C(3)C*H*Me$_2$), 3.61 (3H, s, C(5)O*Me*), 3.71 (1H, d, *J* 2.5, C(6)*H*), 3.79 (3H, s, ArO*Me*), 3.80 (1H, d, *J* 14.7, NC*H*HAr), 5.49 (1H, d, *J* 14.7, NCH*H*Ar), 6.83-6.87 (2H, m, *Ar*), 7.14-7.19 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.8, 17.2, 18.1, 20.4, 26.5, 30.1, 37.3, 45.6, 51.9, 55.2, 60.2, 62.4, 114.0, 128.0, 130.1, 156.1, 159.1, 173.1; *m/*z (ESI$^+$) 347 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{31}N_2O_3$ ([M+H]$^+$) requires 347.2335; found 347.2343.

(3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3,6-di-*iso*-propyl-3-methyl-5-methoxy-3,6-dihydropyrazine-2-one 62



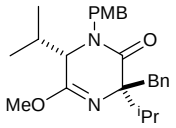
Following *General Procedure 2*, BuLi (2.5 M in hexanes, 1.08 mL, 2.70 mmol), **30** (900 mg, 2.70 mmol), THF (50 mL) and MeI (0.19 mL, 2.97 mmol) gave a 7.5:92.5 mixture of **61**:**62**. Purification *via* flash column chromatography (eluent 3:1 40-60° petrol:Et_2O) gave **62** as a colourless oil (870 mg, 93%, >98% de); $[\alpha]_D^{23}$ –15.8 (*c* 1.15 in $CHCl_3$); ν_{max} (film) 1704, 1644; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.6, C(3)CH*Me*Me), 0.83 (3H, d, *J* 6.8, C(6)CH*Me*Me), 1.01 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.04 (3H, d, *J* 7.1, C(6)CHMe*Me*), 1.28 (3H, s, C(3)*Me*), 2.15-2.25 (1H, m, C(6)C*H*Me_2), 2.25-2.35 (1H, m, C(3)C*H*Me_2), 3.58 (3H, s, C(5)O*Me*), 3.70 (1H, d, *J* 2.8, C(6)*H*), 3.75 (3H, s, ArO*Me*), 3.89 (1H, d, *J* 14.8, NC*H*HAr), 5.43 (1H, d, *J* 14.8, NCH*H*Ar), 6.81-6.84 (2H, m, *Ar*), 7.10-7.14 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.8, 17.2, 18.1, 20.4, 27.8, 29.6, 35.5, 46.0, 51.7, 55.1, 60.5, 63.0 114.0, 128.4, 129.4, 155.9, 159.0, 173.2; *m/*z (ESI^+) 347 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{31}N_2O_3$ ($[M+H]^+$) requires 347.2335; found 347.2335.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 63



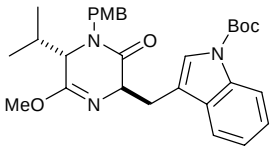
Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.33 mL, 0.53 mmol), **26** (204 mg, 0.53 mmol), THF (10 mL) and ^{i}PrI (60 μL , 0.58 mmol) gave a 98:2 mixture of **63**:**64**. Purification *via* flash column chromatography (eluent 5:1 pentane:Et_2O) gave **63** as a colourless oil (186 mg, 82%, >98% de); $[\alpha]_D^{23}$ +5.1 (*c* 3.4 in $CHCl_3$); ν_{max} (film) 1699, 1634; δ_H (400 MHz, $CDCl_3$) –0.22 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.71 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.83 (3H, d, *J* 7.3, C(6)CHMe*Me*), 1.03 (3H, d, *J* 6.8, C(3)CHMe*Me*), 1.70-1.81 (1H, m, C(6)C*H*Me_2), 2.30-2.41 (1H, m, C(3)C*H*Me_2), 3.01 (1H, d, *J* 12.6, C(3)C*H*HPh), 3.39 (1H, d, *J* 12.6, C(3)CH*H*Ph), 3.60 (1H, d, *J* 2.5, C(6)*H*), 3.69 (3H, s, C(5)O*Me*), 3.79 (3H, s, ArO*Me*), 4.06 (1H, d, *J* 14.9, NC*H*HAr), 5.03 (1H, d, *J* 14.9, NCH*H*Ar), 6.79-6.83 (2H, m, *Ar*), 7.08-7.23 (7H, m, 2 × *Ar*, 5 × *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1, 16.5, 17.9, 20.6, 29.1, 39.1, 43.5, 47.0, 51.9, 55.9, 61.2, 113.7, 126.3, 127.4, 128.2, 128.4, 129.9, 131.3, 138.2, 157.0, 158.8, 171.0; *m/*z (ESI^+) 423 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{35}N_2O_3$ ($[M+H]^+$) requires 423.2648; found 423.2645.

(3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3,6-di-*iso*-propyl-5-methoxy-3,6-dihydropyrazine-2-one 64



Following *General Procedure 2*, BuLi (2.5 M in hexanes, 0.11 mL, 0.27 mmol), **30** (90 mg, 0.27 mmol), THF (10 mL) and BnBr (35 μL, 0.30 mmol) gave a <1:>99 mixture of **63**:**64**. Purification *via* flash column chromatography (eluent 5:1 hexane:Et_2O) gave **64** as a colourless oil (84 mg, 74%, >98% de); $[\alpha]_D^{23}$ +16.4 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 1702, 1644; δ_H (400 MHz, $CDCl_3$) 0.67 (3H, d, *J* 7.0, C(3)CH*Me*Me), 0.84 (3H, d, *J* 7.0, C(3)CHMe*Me*), 0.92 (3H, d, *J* 6.8, C(6)CH*Me*Me), 1.18 (3H, d, *J* 6.8, C(6)CHMe*Me*), 1.86-1.95 (1H, m, C(3)C*H*Me_2), 2.48-2.59 (1H, m, C(6)C*H*Me_2), 2.94 (1H, d, *J* 2.3, C(6)*H*), 2.98 (1H, d, *J* 12.4, C(3)C*H*HPh), 3.16 (1H, d, *J* 12.4, C(3)CH*H*Ph), 3.75 (3H, s, C(5)O*Me*), 3.77 (3H, s, ArO*Me*), 4.18 (1H, d, *J* 15.3, NC*H*HAr), 4.48 (1H, d, *J* 15.3, NCH*H*Ar), 6.60-6.71 (2H, m, *Ar*), 7.09-7.13 (2H, m, *Ar*), 7.20-7.27 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1, 16.4, 19.7, 20.8, 29.1, 36.4, 45.2, 47.7, 51.8, 55.2, 61.5, 68.0, 114.3, 126.2, 127.8, 128.4, 129.1, 130.6, 137.8, 157.4, 158.5, 171.1; *m/z* (ESI^+) 423 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{35}N_2O_3$ ($[M+H]^+$) requires 423.2648; found 423.2646.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-{[*N*(1)′-(*tert*-butyloxycarbonyl)-3′-indoyl]methyl}-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 66



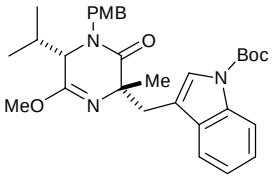
Following *General Procedure 2*, BuLi (2.5 M in hexanes, 1.05 mL, 2.63 mmol), **19** (763 mg, 2.63 mmol), THF (60 mL) and **65** (815 mg, 2.63 mmol) gave a 96.5:3.5 mixture of diastereoisomers. Purification *via* flash column chromatography (eluent 2:1 30-40° petrol:Et_2O) gave the major diastereoisomer **66** as a pale yellow crystalline solid (1.04 g, 76%, >98% de); mp 112-113°C (DCM-heptane); $[\alpha]_D^{24}$ +1.1 (*c* 0.85 in $CHCl_3$); ν_{max} (KBr) 1732, 1698, 1651; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 0.97 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.63 (9H, s, C*Me*$_3$), 2.10-2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.45 (1H, dd, *J* 4.5, 1.0, C(3)C*H*H), 3.47 (1H, dd, *J* 4.5, 1.0, C(3)CH*H*), 3.50 (1H, dd, *J* 3.2, 1.5, C(6)*H*), 3.63 (3H, s, C(5)O*Me*), 3.70 (1H, d, *J* 14.8, NC*H*HAr), 3.74 (3H, s, ArO*Me*), 4.41 (1H, app td, *J* 4.5, 1.5, C(3)*H*), 5.44 (1H, d, *J* 14.8, NCH*H*Ar), 6.66-6.73 (4H, m, *Ar*), 7.21-7.25 (1H, m, C(5′)*H*), 7.27-7.32 (1H, m, C(6′)*H*), 7.51 (1H, s, C(2′)*H*), 7.79 (1H, d, *J* 7.8, C(4′)*H*), 8.17 (1H, br d, *J* 6.1, C(7′)*H*); δ_C (100 MHz, $CDCl_3$) 17.4, 19.5, 28.2, 29.0, 34.1, 46.1, 52.5, 55.1, 58.8, 60.1, 83.1, 114.0, 114.8, 117.3, 120.3, 122.1, 123.9, 124.7, 127.7, 129.0, 131.7, 135.1, 149.7, 159.0, 159.5, 169.4; *m/z* (ESI^+) 542 ($[M+Na]^+$, 100%), 520 (60); HRMS (ESI^+) $C_{30}H_{38}N_3O_5$ ($[M+H]^+$) requires 520.2811; found 520.2811.

X-ray crystal structure determination for 66

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-$K\alpha$ radiation using standard procedures at 190K. The structure was solved by direct methods, all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[3]

X-ray crystal structure data for **66** [$C_{30}H_{37}N_3O_5$]: M = 519.64, monoclinic, space group P 1 21 1, a = 9.3443(3) Å, b = 9.8498(3) Å, c = 15.9297(6) Å, β = 103.8663(15)º, V = 1423.43(8) Å^3, Z = 2, μ = 0.083 mm^{-1}, colourless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm^3. A total of 3279 unique reflections were measured for 5 < θ < 27 and 2832 reflections were used in the refinement. The final parameters were wR_2 = 0.057 and R_1 = 0.052 [$I>\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292510. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-{[*N*(1)′-(*tert*-butyloxycarbonyl)-3′-indoyl]-methyl}-3-methyl-5-methoxy-6-*iso*-propyl-3,6-dihydropyrazine-2-one 67



Following *General Procedure 2*, BuLi (1.6 M in hexanes, 0.50 mL, 0.80 mmol), **66** (415 mg, 0.80 mmol), THF (40 mL) and MeI (50 μL , 0.88 mmol) gave a 97:3 mixture of diastereoisomers. Purification *via* flash column chromatography (eluent 3:1 30-40° petrol:Et_2O) gave the major diastereoisomer **67** as a white crystalline solid (322 mg, 76%, >98% de); mp 84-85°C (DCM-heptane); $[\alpha]_D^{24}$ –4.9 (*c* 2.4 in $CHCl_3$); ν_{max} (KBr) 1732, 1699, 1646; δ_H (400 MHz, $CDCl_3$) 0.30 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 0.89 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.49 (3H, s, C(3)*Me*), 1.67 (9H, s, C*Me*$_3$), 1.87-1.97 (1H, m, CH$_3$C*H*CH$_3$), 3.21 (1H, d, *J* 13.9, C(3)C*H*H), 3.36 (1H, d, *J* 13.9, C(3)CH*H*), 3.60 (3H, s, C(5)O*Me*), 3.67 (1H, d, *J* 2.5, C(6)*H*), 3.79 (3H, s, ArO*Me*), 3.88 (1H, d, *J* 15.0, NC*H*HAr), 5.33 (1H, d, *J* 15.0, NCH*H*Ar), 6.81-6.84 (2H, m, *Ar*), 7.07-7.10 (2H, m, *Ar*), 7.19-7.24 (1H, m, C(5′)*H*), 7.25-7.30 (1H, m, C(6′)*H*), 7.50 (1H, s, C(2′)*H*), 7.69 (1H, d, *J* 7.8,

[3] D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

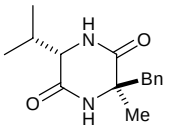
C(4′)*H*), 8.08 (1H, br, d, *J* 7.6, C(7′)*H*); δ_C (100 MHz, $CDCl_3$) 15.7, 20.3, 28.2, 29.7, 30.5, 35.7, 46.4, 52.0, 55.2, 61.0, 61.8, 83.2, 114.1, 114.8, 116.6, 120.4, 122.0, 123.9, 125.2, 128.4, 129.3, 131.8, 134.7, 150.3, 156.0, 159.0, 172.3; *m/z* (ESI^+) 556 ($[M+Na]^+$, 100%), 354 (80); HRMS (ESI^+) $C_{31}H_{40}N_3O_5$ ($[M+H]^+$) requires 534.2968; found 534.2966.

X-ray crystal structure determination for 67

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-$K\alpha$ radiation using standard procedures at 190K. The structure was solved by direct methods, all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

X-ray crystal structure data for **67** [$C_{31}H_{43}N_3O_7$]: M = 569.70, orthorhombic, space group P 21 21 21, a = 9.4150(1) Å, b = 33.8450(4) Å, c = 9.5680(2) Å, V = 3048.85(8) $Å^3$, Z = 4, μ = 0.088 mm^{-1}, colourless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm^3. A total of 3860 unique reflections were measured for $5 < \theta < 27$ and 3329 reflections were used in the refinement. The final parameters were wR_2 = 0.072 and R_1 = 0.072 [$I>\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292511. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

(3*R*,6*S*)-3-Benzyl-3-methyl-6-*iso*-propyl-piperazine-2,5-dione 68



Following *General Procedure 3*, **59** (1.29 g, 3.26 mmol) and TFA (50 mL) gave **68** as an off white solid (509 mg, 60%); mp 280-282°C; $[\alpha]_D^{23}$ –22.0 (*c* 0.9 in CH_3CO_2H); ν_{max} (KBr) 3193, 1670; δ_H (400 MHz, DMSO-d_6) 0.70 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.78 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.42 (3H, s, C(3)*Me*), 1.93-2.02 (1H, m, CH$_3$C*H*CH$_3$), 2.67 (1H, dd, *J* 2.5, 1.7, C(6)*H*), 2.67 (1H, d, *J* 12.9, C(3)C*H*HPh), 3.08 (1H, d, *J* 12.9, C(3)CH*H*Ph), 7.11-7.15 (2H, m, *Ph*), 7.22-7.26 (3H, m, *Ph*), 7.76 (1H, app br s, N(1)*H*), 8.24 (1H, app br s, N(4)*H*); δ_C (100 MHz, DMSO-d_6) 17.3, 18.9, 28.6, 31.8, 47.3, 59.6, 60.4, 127.6, 128.7, 131.1, 137.0,

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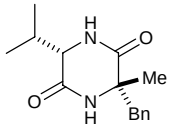
[4] D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

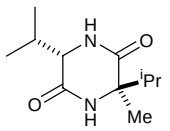
167.1, 170.4; *m/*z (CI^+) 261 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{15}H_{21}N_2O_2$ ($[M+H]^+$) requires 261.1603; found 261.1610.

(3*S*,6*S*)-3-Benzyl-3-methyl-6-*iso*-propyl-piperazine-2,5-dione 69



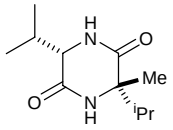
Following *General Procedure 3*, **60** (775 mg, 1.96 mmol) and TFA (40 mL) gave **69** as an off white solid (459 mg, 66%); mp 283-285°C; $[\alpha]_D^{23}$ –11.7 (*c* 1.1 in AcOH); ν_{max} (KBr) 1656; δ_H (400 MHz, DMSO-d_6) 0.11 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.57 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.44 (3H, s, C(3)*Me*), 1.66-1.74 (1H, m, CH$_3$C*H*CH$_3$), 2.61 (1H, d, *J* 13.1, C(3)C*H*HPh), 3.19 (1H, d, *J* 13.1, C(3)CH*H*Ph), 3.59 (1H, dd, *J* 3.3, 1.8, C(6)*H*), 7.12-7.23 (5H, m, *Ph*), 7.72 (1H, app br s, N(1)*H*), 8.21 (1H, br, s, N(4)*H*); δ_C (100 MHz, DMSO-d_6) 16.6, 18.8, 30.4, 31.5, 45.3, 59.8, 60.6, 127.3, 128.6, 131.4, 137.5, 166.7, 170.0; *m/*z (CI^+) 261 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{15}H_{21}N_2O_2$ ($[M+H]^+$) requires 261.1603; found 261.1607.

(3*R*,6*S*)-3,6-Di-*iso*-propyl-3-methyl-piperazine-2,5-dione 70



Following *General Procedure 3*, **61** (970 mg, 2.80 mmol) and TFA (50 mL) gave **70** an off white solid (423 mg, 71%); mp 287°C (sub); $[\alpha]_D^{24}$ +220 (*c* 0.4 in AcOH); ν_{max} (KBr) 3196, 1666; δ_H (400 MHz, DMSO-d_6) 0.82 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.82 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.85 (3H, d, *J* 6.8, C(3)CHMe*Me*), 0.94 (3H, d, *J* 7.1, C(6)CHMe*Me*), 1.90-1.99 (1H, m, C(3)C*H*Me$_2$), 2.18-2.26 (1H, m, C(6)C*H*Me$_2$), 3.75 (1H, dd, *J* 2.0, 1.8, C(6)*H*), 7.88 (1H, app br s, N(1)*H*), 8.02 (1H, br s, N(4)*H*); δ_C (100 MHz, DMSO-d_6) 16.6, 17.3, 18.3, 19.0, 25.3, 32.2, 37.9, 59.8, 61.4, 167.7, 171.3; *m/*z (CI^+) 213 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{11}H_{21}N_2O_2$ ($[M+H]^+$) requires 213.1603; found 213.1604.

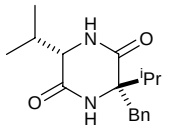
(3*S*,6*S*)-3,6-Di-6-*iso*-propyl-3-methyl-piperazine-2,5-dione 71



Following *General Procedure 3*, **62** (540 mg, 1.56 mmol) and TFA (40 mL) gave **71** an off white solid (290 mg, 87%); mp 289-290°C; $[\alpha]_D^{23}$ +101 (*c* 0.4 in AcOH); ν_{max} (KBr) 3190, 1663; δ_H (400 MHz, DMSO-d_6)

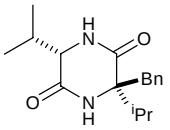
0.82 (3H, d, *J* 6.8, C(3)CH*Me*Me), 0.83 (3H, d, *J* 6.8, C(6)CH*Me*Me), 0.88 (3H, d, *J* 7.1, C(3)CHMe*Me*), 0.96 (3H, d, *J* 7.3, C(6)CHMe*Me*), 1.27 (3H, s, C(3)*Me*), 2.00-2.08 (1H, m, C(3)C*H*Me$_2$), 2.14-2.27 (1H, m, C(6)C*H*Me$_2$), 3.79 (1H, dd, *J* 2.7, 1.5, C(6)*H*), 7.81 (1H, app br s, N(1)*H*), 7.84 (1H, br s, N(4)*H*); δ_C (100 MHz, DMSO-d_6) 16.5, 18.0, 19.0, 19.3, 25.7, 31.6, 36.0, 59.7, 61.5, 167.8, 171.5; *m/z* (CI$^+$) 213 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{10}H_{21}N_2O_2$ ([M+H]$^+$) requires 213.1603; found 213.1610.

(3*R*,6*S*)-3,6-Di-*iso*-propyl-3-benzyl-piperazine-2,5-dione 72



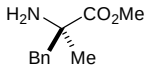
Following *General Procedure 3*, **63** (1.21 g, 2.86 mmol) and TFA (50 mL) gave **72** an off white solid (547 mg, 66%); mp 309°C (sub); $[\alpha]_D^{24}$ +84.2 (*c* 0.4 in AcOH); ν_{max} (KBr) 3192, 1658; δ_H (500 MHz, CF_3CO_2D) 0.25 (3H, d, *J* 7.0, C(6)CH*Me*Me), 1.01 (3H, d, *J* 7.3, C(6)CHMe*Me*), 1.23 (3H, d, *J* 6.7, C(3)CH*Me*Me), 1.32 (3H, d, *J* 7.0, C(3)CHMe*Me*), 2.12-2.19 (1H, m, C(6)C*H*Me$_2$), 2.56-2.65 (1H, m, C(3)C*H*Me$_2$), 3.18 (1H, d, *J* 14.0, C(3)C*H*HPh), 3.59 (1H, d, *J* 14.0, C(3)CH*H*Ph), 4.22 (1H, d, *J* 3.4, C(6)*H*), 7.30-7.45 (5H, m, *Ph*); δ_C (125 MHz, CF_3CO_2D) 15.8, 16.2, 18.3, 19.1, 33.3, 40.3, 44.2, 61.8, 71.0, 130.1, 131.1, 132.6, 136.2, 174.2, 174.8; *m/z* (CI$^+$) 289 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{17}H_{25}N_2O_2$ ([M+H]$^+$) requires 289.1916; found 289.1909.

(3*S*,6*S*)-3,6-Di-*iso*-propyl-3-benzyl-piperazine-2,5-dione 73



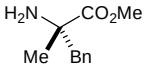
Following *General Procedure 3*, **64** (390 mg, 0.92 mmol) and TFA (30 mL) gave **73** as an off white solid (230 mg, 86%); mp 324°C (sub); $[\alpha]_D^{23}$ –20.5 (*c* 0.4 in AcOH); ν_{max} (KBr) 3191, 1667; δ_H (400 MHz, CF_3CO_2D) 0.98 (3H, d, *J* 6.9, C(6)CH*Me*Me), 1.04 (3H, d, *J* 6.9, C(6)CHMe*Me*), 1.20 (3H, d, *J* 6.5, C(3)CH*Me*Me), 1.33 (3H, d, *J* 6.9, C(3)CHMe*Me*), 2.39-2.46 (1H, m, C(6)C*H*Me$_2$), 2.69-2.75 (1H, m, C(3)C*H*Me$_2$), 2.96 (1H, app d, *J* 2.3, C(6)*H*), 3.25 (1H, d, *J* 13.9, C(3)C*H*HPh), 3.36 (1H, d, *J* 13.9, C(3)CH*H*Ph), 7.26-7.29 (2H, m, *Ph*), 7.39-7.46 (3H, m, *Ph*); δ_C (100 MHz, CF_3CO_2D) 15.9, 16.8, 19.1, 19.7, 33.0, 37.0, 46.8, 61.6, 71.2, 130.4, 131.1, 132.5, 135.7, 175.1, 175.6; *m/z* (CI$^+$) 289 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{17}H_{25}N_2O_2$ ([M+H]$^+$) requires 289.1916; found 289.1907.

(*R*)-α-Methyl-phenylalanine methyl ester (*R*)-75



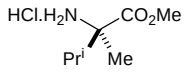
Following *General Procedure 4*, **68** (297 mg, 1.14 mmol) and conc HCl (35 mL) gave a mixture of amino acid hydrochloride salts **35** and (*R*)-**74** (360 mg); δ_H (400 MHz, MeOD) 1.12 (6H, d, *J* 6.8, C*H*$_3$CHC*H*$_3$), 1.66 (3H, s, C*Me*), 2.30-2.39 (1H, m, CH$_3$C*H*CH$_3$), 3.16 (1H, d, *J* 14.3, C*H*HPh), 3.33 (1H, d, *J* 14.3, CCH*H*Ph), 3.89 (1H, d, *J* 4.4, ^{i}PrC*H*), 7.29-7.41 (5H, m, *Ph*). Subsequently, following *General Procedure 5*, the mixture of amino acid hydrochloride salts **35** and **74** (360 mg), $SOCl_2$ (0.21 mL, 2.75 mmol) and MeOH (40 mL) gave a mixture of amino acid methyl ester hydrochloride salts, which was neutralized and distilled to give (*R*)-**75** as a colourless oil (166 mg, 66%); $[\alpha]_D^{24}$ +11.9 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3368, 1734; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, C*Me*), 2.82 (1H, d, *J* 13.1, C*H*HPh), 3.09 (1H, d, *J* 13.1, CH*H*Ph), 3.68 (3H, s, O*Me*), 4.81 (2H, br s, N*H*$_2$), 7.12-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.9, 46.2, 51.6, 58.8, 127.1, 128.4, 130.0, 136.6, 176.8; *m/z* (ESI$^+$) 194 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{16}NO_2$ ([M+H]$^+$) requires 194.1181; found 194.1182.

(*S*)-α-Methyl-phenylalanine methyl ester (*S*)-75



Following *General Procedure 4*, **69** (266 mg, 1.02 mmol) and conc HCl (30 mL) gave a mixture of amino acid hydrochloride salts **35** and (*S*)-**74** (351 mg). Subsequently, following *General Procedure 5*, the mixture of amino acid hydrochloride salts **35** and (*S*)-**74** (351 mg), $SOCl_2$ (0.04 mL, 0.73 mmol) and MeOH (10 mL) gave a mixture of methyl ester hydrochloride salts, which was neutralization and distilled to give (*S*)-**75** as a colourless oil (129 mg, 74%); $[\alpha]_D^{23}$ –14.1 (*c* 1.6 in $CHCl_3$).

(*R*)-α-Methyl-valine methyl ester hydrochloride (*R*)-80

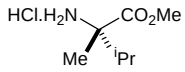


Following *General Procedure 4*, **55** (390 mg, 1.62 mmol) in conc HCl (30 mL) gave a mixture of amino acid hydrochloride salts **77** and (*R*)-**78** (539 mg); δ_H (400 MHz, MeOD) 1.04-1.10 (9H, m, C*H*$_3$CHC*H*$_3$, C*H*$_3$CHCH$_3$), 1.17 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.55 (3H, s, C*Me*), 2.16-2.26 (1H, m, CH$_3$C*H*CH$_3$), 2.32-2.41 (1H, m, CH$_3$C*H*CH$_3$), 2.77 (3H, s, NC*H*$_3$), 3.89 (1H, d, *J* 3.8, ^{i}PrC*H*). Subsequently, following *General Procedure 11*, the mixture of amino acid salts **77** and (*R*)-**78** (539 mg), $SOCl_2$ (2 mL, 27.4 mmol) and MeOH (50 mL) gave a mixture of methyl ester hydrochloride salts which was neutralised according to *General Procedure 5*, separated *via* flash column chromatography (eluent 3:1 30-40° petrol:Et_2O) and re-acidified to give **79** as a white solid (first to elute, 238 mg, 81%) and (*R*)-**80** as a white solid (second to elute, 231 mg, 80%).

Data for **79:** mp 103-104˚C; $[\alpha]_D^{22}$ +19.9 (*c* 0.85 in MeOH); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.14 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.50-2.61 (1H, m, CH$_3$C*H*CH$_3$), 2.74 (3H, s, N*Me*), 3.60 (1H, d, *J* 4.5, ^{i}PrCH), 3.83 (3H, s, O*Me*), 4.81 (2H, br s, N*H*$_2$).

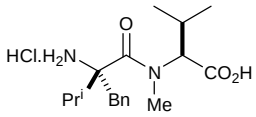
Data for (*R*)-**80**: mp 143-144˚C; $[\alpha]_D^{22}$ –4.3 (*c* 0.65 in MeOH); ν_{max} (KBr) 1750; δ_H (400 MHz, MeOD) 1.08-1.15 (6H, m, C*H*$_3$CHC*H*$_3$), 1.69 (3H, s, C*Me*), 2.23-2.32 (1H, m, CH$_3$C*H*CH$_3$), 3.82 (3H, s, O*Me*); δ_C (100 MHz, MeOD) 16.8, 17.6, 20.1, 37.5, 53.0, 64.2, 170.7; *m/z* (ESI$^+$) 146 ([M–Cl]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{16}NO_2$ (M–Cl]$^+$) requires 146.1181; found 146.1182.

(*S*)-α-Methyl-valine methyl ester hydrochloride (*S*)-80



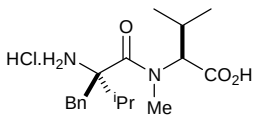
Following *General Procedure 4*, **56** (416 mg, 1.73 mmol) in conc HCl (30 mL) gave a mixture of amino acid hydrochloride salts **77** and (*S*)-**78** (575 mg). Subsequently, following *General Procedure 5*, the mixture of amino acid salts **77** and (*S*)-**78** (575 mg), $SOCl_2$ (2 mL, 27.4 mmol) and MeOH (50 mL) gave a mixture of methyl ester hydrochloride salts which was neutralised according to *General Procedure 5*, separated *via* flash column chromatography (eluent 3:1 30-40° petrol:Et_2O) and re-acidified to give **79** as a white solid (first to elute, 236 mg, 75%) and (*R*)-**80** as a white solid (second to elute, 217 mg, 69%); $[\alpha]_D^{22}$ +4.5 (*c* 1.2 in MeOH).

HN[(*R*)-α-Benzyl-valine][(*S*)-*N*-methyl-valine]OH hydrochloride 81



A solution of **57** (537 mg, 1.70 mmol) in conc HCl (30 mL) was subjected to reflux for 16 h before being concentrated *in vacuo*. This process was repeated 6 times. The residue was then dried under high vacuum to give **81** (590 mg, 97%); mp 158-159°C; $[\alpha]_D^{22}$ +6.1 (*c* 2.5 in $CHCl_3$); ν_{max} (KBr) 1718, 1628; δ_H (400 MHz, MeOD) 1.08 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.12 (3H, d, *J* 7.1, C*H*$_3$CHCH$_3$), 1.14 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.15 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.21-2.32 (2H, m, 2 × CH$_3$C*H*CH$_3$), 2.71 (3H, s, N*Me*), 3.04 (1H, d, *J* 14.1, C*H*HPh), 3.35 (1H, d, *J* 14.1, CH*H*Ph), 3.39 (1H, d, *J* 3.8, ^{i}PrC*H*), 7.21-7.38 (5H, m, *Ph*); δ_C (100 MHz, MeOD) 15.9, 17.1, 17.4, 18.1, 23.7, 32.7, 34.0, 40.1, 69.7, 93.7, 127.6, 128.8, 130.5, 135.0, 168.4, 176.2; *m/z* (ESI$^+$) 321 ([M–Cl]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{29}N_2O_3$ ([M–Cl]$^+$) requires 321.2178; found 321.2182.

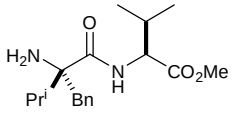
HN[(*S*)-α-Benzyl-valine][(*S*)-*N*-methyl-valine]OH hydrochloride 82



A solution of **58** (412 mg, 1.30 mmol) in conc HCl (30 mL) was subjected to reflux for 16 h before being concentrated *in vacuo*. This process was repeated 6 times. The residue was then dried under high vacuum to give **82** as a pale yellow crystalline solid (460 mg, 99%); mp 175-177°C; $[\alpha]_D^{23}$ –31.2 (*c* 0.6 in CH_3OH); ν_{max} (KBr) 1672, 1641; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.8, CH(C*H*$_3$CHCH$_3$)), 0.98 (3H, d, *J* 6.8,

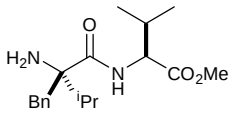
C(C*H*$_3$CHCH$_3$)), 1.04 (3H, d, *J* 7.1, CH(CH$_3$CHC*H*$_3$)), 1.10 (3H, d, *J* 7.1, C(CH$_3$CHC*H*$_3$)), 2.07-2.17 (1H, m, CH(CH$_3$C*H*CH$_3$)), 2.41-2.49 (1H, m, C(CH$_3$C*H*CH$_3$)), 2.60 (3H, s, N*Me*), 2.63 (1H, d, *J* 3.0, ^{i}PrC*H*), 2.97 (1H, d, *J* 13.0, C*H*HPh), 3.01 (1H, d, *J* 13.0, CH*H*Ph), 7.10-7.16 (2H, m, *Ph*), 7.24-7.29 (3H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1, 16.4, 18.7, 19.3, 30.9, 32.9, 35.7, 46.0, 66.2, 96.1, 127.3, 128.1, 130.7, 135.9, 168.4, 168.7; *m/z* (ESI$^+$) 321 ([M−Cl]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{29}N_2O_3$ ([M–Cl]$^+$) requires 321.2178; found 321.2163.

HN[(*R*)-α-Benzyl-valine][(*S*)-valine]OMe 83



CAN (90 mg, 0.15 mmol) was added to a solution of **63** (23 mg, 0.05 mmol) in MeCN (3.5 mL) and H_2O (1.5 mL). The resultant mixture was stirred at rt for 16 h then quenched with sat aq K_2CO_3 solution. H_2O was then added followed by an organic extraction with DCM. The organic extract was dried and concentrated *in vacuo* to give **83** as a colourless oil (18 mg, 80%); ν_{max} (film) 1699, 1664; δ_H (400 MHz, $CDCl_3$) 0.69 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.74 (3H, d, *J* 7.2, C*H*$_3$CHCH$_3$), 0.80 (3H, d, *J* 6.5, C*H*$_3$CHCH$_3$), 1.13 (3H, d, *J* 6.5, C*H*$_3$CHCH$_3$), 2.01-2.10 (1H, m, CH$_3$C*H*CH$_3$), 2.47-2.56 (1H, m, CH$_3$C*H*CH$_3$), 2.92 (1H, d, *J* 12.6, C*H*HPh), 3.07 (1H, d, *J* 12.6, CH*H*Ph), 3.76 (3H, s, O*Me*), 3.80 (1H, m, ^{i}PrC*H*), 5.44 (1H, app br s, CON*H*), 7.07-7.23 (5H, m, *Ph*), 7.27 (2H, s, N*H*$_2$); *m/*z (ESI$^+$) 321 ([M+H]$^+$, 100 %); HRMS (ESI$^+$) $C_{18}H_{29}N_2O_3$ ([M+H]$^+$) requires 321.2178; found 321.2176.

HN[(*S*)-α-Benzyl-valine][(*S*)-valine]OMe 84



CAN (230 mg, 0.42 mmol) was added to a solution of **64** (59 mg, 0.14 mmol) in MeCN (3.5 mL) and H_2O (1.5 mL). The resultant mixture was stirred at rt for 16 h then quenched with sat aq K_2CO_3 solution. H_2O was then added followed by an organic extraction with DCM. The organic extract was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 2:98 MeOH:$CHCl_3$) gave **84** as a colourless oil (30 mg, 67%); $[\alpha]_D^{24}$ +44.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1699, 1665; δ_H (400 MHz, $CDCl_3$) −0.07 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.68 (3H, d, *J* 7.3, CH$_3$CHC*H*$_3$), 0.85 (3H, d, *J* 6.6, C*H*$_3$CHCH$_3$), 1.06 (3H, d, *J* 6.6, CH$_3$CHC*H*$_3$), 1.80-1.89 (1H, m, CH$_3$C*H*CH$_3$), 2.25-2.35 (1H, m, CH$_3$C*H*CH$_3$), 2.95 (1H, d, *J*

12.5, C*H*HPh), 3.31 (1H, d, *J* 12.5, CH*H*Ph), 3.74 (3H, s, O*Me*), 3.75 (1H, m, ^{i}PrC*H*), 5.93 (1H, br d, *J* 8.6, CON*H*), 7.12-7.14 (5H, m, *Ph*), 7.16 (2H, s, NH_2); δ_C (100 MHz, $CDCl_3$) 14.3, 16.1, 18.0 (2C), 30.0, 37.9, 43.1, 52.7, 57.6, 67.9, 126.1, 127.7, 131.1, 137.8, 156.9, 172.6; *m/*z (ESI$^+$) 321 ($[M+H]^+$, 100%); HRMS $C_{18}H_{29}N_2O_3$ ($[M+H]^+$) requires 321.2178; found 321.2176.